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Quantumchemical Structure of Carcinogenic Benz[*c*]acridines

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Abstract. *Resonance energies, circuit resonance energies and bond currents of benz[c]acridines were calculated by Aihara's TRE theory. Consequently, it was shown that these compounds had very stable aromatic characters with positive resonance energies and that the resonance energies per π-electron values for the compounds with lack of the double bond corresponding to the K-region from parent skeleton were more stable than those of their parent compounds. Carcinogenic activity of the compounds was related to the charge at QK, QN and QL and high electron density on HOMO orbital.*

Benz[c]acridines have been found to be carcinogenic (1,2). The relation between carcinogenic activity and the physical and chemical properties of angular benzacridines has been studied (3). We investigated the relationship between the carcinogenic activity of benz[c]acridines and their resonance energy (RE), measured by the Hückel orbital molecular method (HMO). Aihara's theory of aromaticity was adopted to delineate the resonance energy (RE), resonance energy per π-electron (REPE), circuit resonance energy (CRE), circuit current (CC) and bond current (BC) for estimating QSAR (4-8).

Materials and Methods

Materials. All benz[c]acridine-related compounds used in this paper were prepared as described previously (Figure 1) (9).

Calculations. Benz[c]acridine (**1**) has a system possessing 18 orbitals and 18π-electrons, and their electronic distribution can be calculated by HMO and modified-neglect-of-diatomic overlap (MNDO) method. The HMO theory is assumed in its simplest form. Usually, the Coulomb and the resonance integrals in the Hückel method are given as follows (10).

$$\alpha_x = \alpha + h_{x\beta} \quad \beta_{cx} = l_{c\times\beta}$$

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Key Words: Benz[c]acridines, MNDO, π-electron density of K,L,M-regions.

where α and ß are Coulomb and resonance integrals of benzene, respectively. Streitwieser evaluated the heteroatom parameters for the amine nitrogen, the imine nitrogen, the ether oxygen and the ketone oxygen (10). In this paper, we adopted these values with some other heteroatom parameters for QSAR (Table I) (11).

Aihara recently developed a general graph theoretical formula for the RE, CRE, and BC (4-8). Many examples indicate that the graph theory of aromaticity has been one of the most important principles in the study of aromaticity. Kurihara *et al* (12) reported that the fundamental skeleton of the tropones possessing a unique heptagonal structure could be predicted to be aromatic with positive RE.

The reactivity indices used for comparing the carcinogenic activity are the frontier electron density and the approximate superdelocalizability of the carbon atom to which the K-, and M-region are attached.

The MNDO, RE, CRE and CC calculations of benz[c]acridines were calculated by Aihara's graph theory of aromaticity, using a FACOM 360 Computer in the Josai University Information Sciences Center.

Results and Discussion

*MNDO optimized geometries of benz[c]*acridines. The MNDO is a resonably reliable method for the prediction of heats of formation and molecular geometries of many organic molecules.

The geometry optimizations of benz[c]acridine (**1**) and its eleven methylated benz[c]acridines (**2-12**) were carried out with optimization of all geometrical parameters with no assumptions. In all benz[c]acridines (**1-12**), the MNDO optimized geometries were planar, and structures are shown in Figures 2-4. The C-C bonds of benz[c]acridine (**1**) were 1.41-1.48Å except for the C_{12a}-C_{6a} bond which was 1.45Å, and the formular double bonds were 1.36-1.40Å except for the central bonds such as C_{11a}-C_{7a} which were 1.431-1.430Å. The C_{11a}-N_{12} and N_{12}-C_{12a} were 1.36Å and 1.345Å, respectively. The C-C bonds of methyl-substituted benz[c]acridines (**2-12**) were 1.41-1.48Å except for the C_{12a}-C_{6a} bond which were 1.446-1.458Å, and the formular double bonds were 1.36-1.40Å except the central bonds such C_{11a}-C_{7a} which were 1.431-1.447Å. The C_{11a}-N_{12} and N_{12}-C_{12a} were 1.362-1.368Å and 1.338-1.346Å, respectively. In all cases, the C_5-C_6 were characteristically shorter than the other double bonds.

*MNDO calculation values of benz[c]*acridines. The MNDO

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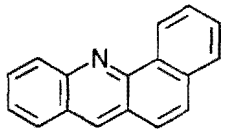
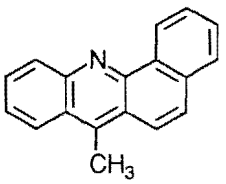
Benz[*c*]acridine

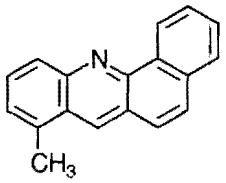


benz[*c*]acridine (**1**)

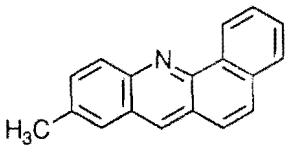
Monomethylbenz[*c*]acridines



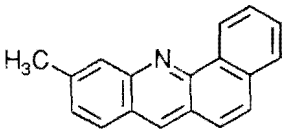
7-methylbenz[*c*]acridine (**2**)



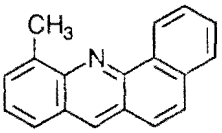
8-methylbenz[*c*]acridine (**3**)



9-methylbenz[*c*]acridine (**4**)

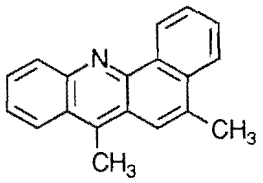


10-methylbenz[*c*]acridine (**5**)

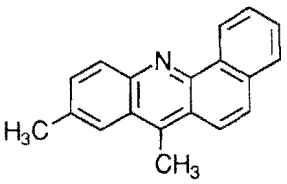


11-methylbenz[*c*]acridine (**6**)

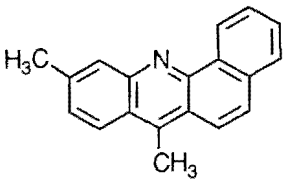
Dimethylbenz[*c*]acridines



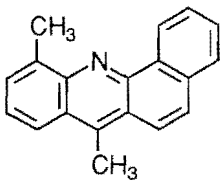
5,7-dimethylbenz[*c*]acridine (**7**)



7,9-dimethylbenz[*c*]acridine (**8**)

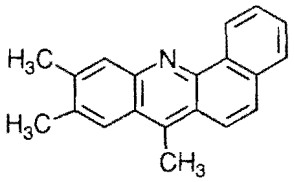


7,10-dimethylbenz[*c*]acridine (**9**)

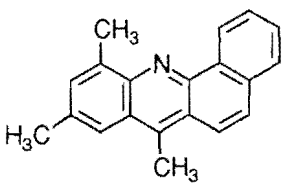


7,11-dimethylbenz[*c*]acridine (**10**)

Trimethylbenz[*c*]acridines



7,9,10-trimethylbenz[*c*]acridine (**11**)



7,9,11-trimethylbenz[*c*]acridine (**12**)

Figure 1. *Twelve benz[c]acridines (1-12) used in this study.*

Table I. *Heteroatom parameters*

$h_N^+ = 0.5$	$k_{C-N} = 1.0$
$h_N = 1.5$	$k_{C-N} = 0.8$
$h_N^+ = 2.0$	
$h_O = 2.0$	$k_{C-O} = 0.8$
$h_O^+ = 1.0$	$k_{C-O} = 1.0$
$h_O^+ = 2.5$	
$h_S^+ = 1.0$	$k_{C-S} = 0.68$
$h_S^+ = 0.9$	$k_{C-S} = 1.2$

calculation values of benz[*c*]acridine (**1**) and its methylated benz[*c*]acridines (**2-12**) are given in Tables II-VI.

(1) MNDO calculations and half-wave potentials: Table II shows the π-electron highest occupied molecular orbital/π-electron lowest unoccupied molecular orbital (π-LUMO) gap, orbital energies of π-LUMO and π-HOMO, lone pair energy (n_O), half-peak wave oxidation potential ($E^{ox}_{p/2}$), and half-wave reduction potential ($E^{red}_{1/2}$), on benz[*c*]acridines (**1-12**). By Koopmans' theory (13), the electron affinity (EA) of a compound should be equal to the negativity of its π-LUMO energies. In a previous paper, we reported the $E^{ox}_{p/2}$ and $E^{red}_{1/2}$ values of benz[*c*]acridines (**1-12**) (14). The plot of $E^{red}_{1/2}$, against π-LUMO energies ε_{LUMO} on benz[*c*]acridines (**1-12**) is shown in Figure 5. There is a linear correlation between the $E^{red}_{1/2}$, against ε_{LUMO} on benz[*c*]acridines (**1-12**). The method of least-squares yielded the correlation equation 1.

$$E^{red}_{1/2}\ (v) = 2.0474\ (\varepsilon_{LUMO}) + 0.24823 \qquad (1)$$

It should be noted in Figure 5 that the benz[*c*]acridines are grouped in such a way that the compounds which have negative ($E^{red}_{1/2}$) values, that is higher ε_{LUMO}, are carcinogenic and the benz[*c*]acridines which have relatively positive $(E^{red})_{1/2}$ values, that is lower ε_{LUMO}, are noncarcinogenic except 5,7-dimethylbenz[*c*]acridine (**7**). It was suggested that the anomalous behaviour of 5,7-dimethylbenz[*c*]acridine (**7**) could be caused by a steric hindrance due to substitution in the phenanthrenoid bond, which might influence any activity (15).

The plot of $E^{ox}_{p/2}$ against the calculated π-HOMO energies (ε_{HOMO}) gave a straight line, which is shown in Figure 6. A least-squares correlation gave equation 2.

$$E^{ox}_{p/2}\ (v) = -3.0375\ \varepsilon_{HOMO} - 24.0000 \qquad (2)$$

(2) π-LUMO and π-HOMO coefficients: Nucleophilic and electrophilic attack on a benz[*c*]acridine should be favored at the atom with the largest π-LUMO and π-HOMO coefficient, respectively. Table III shows the π-LUMO coefficients of the benz[*c*]acridines. Therefore, a nucleophilic attack should occur on position 7 in each benz[*c*]acridine because positions 7 has larger π-LUMO coefficients than any other positions of benz[*c*]acridines. In Table IV, the π-HOMO coefficient magnitudes of methylated benz[*c*]acridines are in the order of C-6 > C-5 > or C-7 (16). Table V shows the electron density of benz[*c*]acridines (**1-12**). The carcinogenic activity appeared to be also related to the electron densities on position C-7, which were divided into the carcinogenic group (**2,8-12**) with the increasing electron density (4.002) except compound **7**, and the noncarcinogenic group (**1,3-6**) with decreasing electron density (3.970). Table VI shows the π-electron density of benz[*c*]acridines (**1-12**). The relationship between their π-electron density on position C-7, and carcinogenic activity was similar to the trend of their electron density and carcinogenic activity in Table V. The benz[*c*]acridines (**1-12**) were divided into a carcinogenic group (**2,8-12**) with increasing π-electron density (0.944) on position C-7, and a noncarcinogenic group (**1,3-7**) with decreasing electron density (0.943).

(3) Electronic spectra: All benz[*c*]acridines (**1-12**) exhibited absorption bands with a large intensity (ε < 40000) in the wavelength region of 260-300 nm and their methylated benz-[*c*]acridines had very similar absorption bands. For example, benz[*c*]acridine (**1**) showed absorption bands at 224 (ε = 38800), 276 (ε = 66500), 287 (ε = 56500) and 336 nm (ε = 5300). This means that the π-HOMO/LUMO gap is related to the energy of the $\pi \rightarrow \pi^*$ electron transition from these data (Table II).

We have also calculated the electronic transition of these compounds by the complete-neglect-of-differential overlap/S-configuration interaction (CNDO/S-CI) method (17,18). The CNDO/S-CI calculation was adopted on these MNDO optimized geometries. The coefficient distributions of the four highest occupied and the four lowest unoccupied π orbitals are shown in Figure 7. Because their coefficients were similar, the predictably calculated electronic transitions had a similarity on two adsorption bands. The calculated electronic transitions for benz[*c*]acridine (**1**) are shown in Table VII. The benz[*c*]acridine (**1**) showed $\pi \rightarrow \pi^*$ electronic transition at 3.60, 3.93, 4.13, 4.47, 4.60, 4.90, 5.02, 5.20, 5.67, 5.896 and 5.98 eV in the region of 260-360 nm, corresponding to π_1-π_1^* and π_1-π_2^*.

From the coefficient distribution as shown in Figure 7, these bands could be attributed to an intramolecular charge transfer transition from the benzene ring part or peripheral ring part to the benzene ring part or peripheral ring part. The CNDO/S-CI calculations satisfactorily reproduced the red shift observed in the wavelength region of 260-360 nm of benz[*c*]acridine (**1**) and its methylated benz[*c*]acridines **2-12**).

(4) Calculation of RE and heats of formation of benz[c]acridines (**1-12**)**:** The calculated heats of formation and REs for a series of benz[*c*]acridines (**1-12**) are given in Table VIII. Benz[*c*]acridines (**1-12**) had very stable aromatic characters with positive resonance energies.

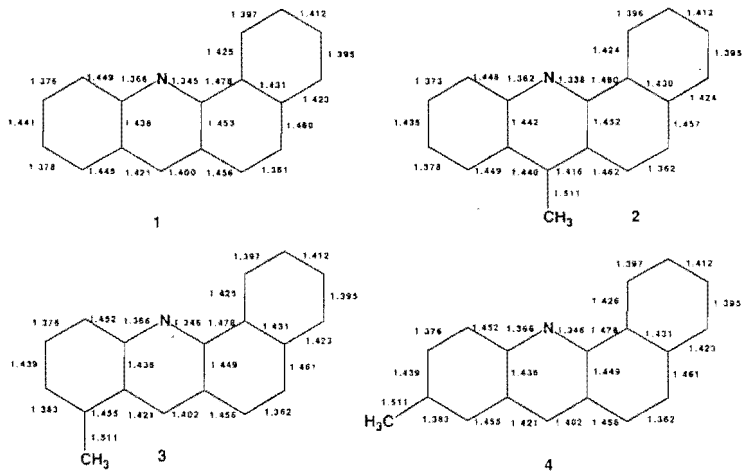


Figure 2. *MNDO optimized geometries of benz[c]acridines* ***(1-4)****. Bond lengths are expressed in Angstroms (Å).*

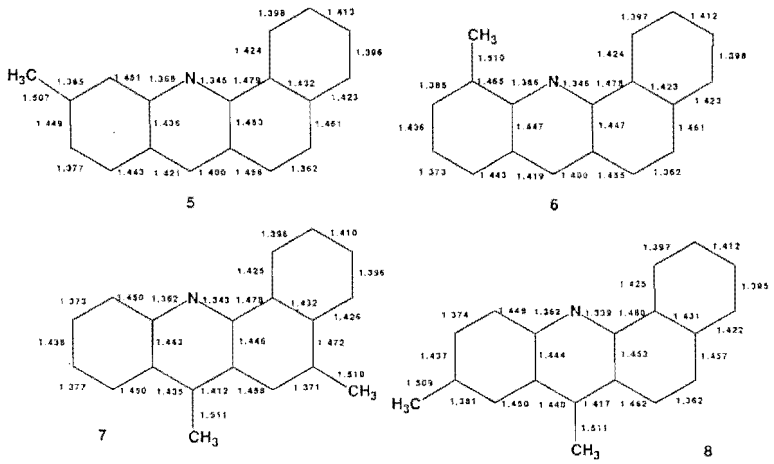


Figure 3. *MNDO optimized geometries of benz[c]acridines* ***(5-8)****. Bond lengths are expressed in Angstroms (Å).*

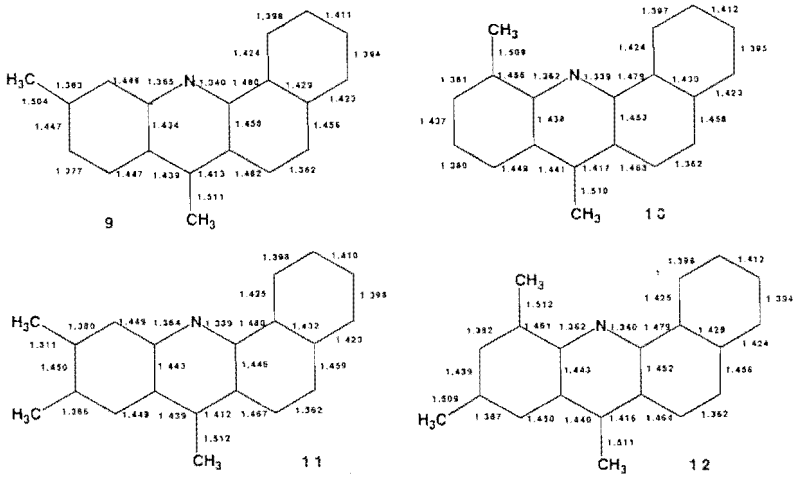


Figure 4. *MNDO optimized geometries of benz[c]acridines* ***(9-12)****. Bond lengths are expressed in Angstroms (Å).*

Table II. *Results of MNDO calculations and half-wave potentials on the benz[c]acridines (1-12).*

Compd. No.	π-HOMO/π-LUMO (gap, eV)	π-LUMO (eV)	π-HOMO (eV)	$E^{red}_{1/2}$ (V *vs.* SCE)[a,b]	$E^{ox}_{d/2}$ (V *vs.* SCE)[b,c]	n_o (eV)[d]
1	7.474	-0.981	-8.455	-1.77	1.59	-10.694
2	7.387	-1.036	-8.423	-1.87	1.50	-10.663
3	7.443	-1.005	-8.448	-1.74	1.51	-10.726
4	7.456	-0.996	-8.452	-1.82	1.58	-10.736
5	7.454	-0.989	-8.443	-1.82	1.53	-10.714
6	7.440	-1.001	-8.441	-1.76	1.52	-10.686
7	7.356	-1.057	-8.413	-1.89	1.46	-10.673
8	7.371	-1.050	-8.421	-1.91	1.48	-10.667
9	7.371	-1.047	-8.418	-1.87	1.43	-10.688
10	7.360	-1.049	-8.409	-1.89	1.49	-10.610
11	7.378	-1.045	-8.423	-1.92	1.39	-10.647
12	7.334	-1.070	-8.404	-1.97	1.41	-10.656

[a] Half-wave reduction potential: [b] ref. 14:
[c] Half-peak wave oxidation potential: [d] n^o: Lone pair energies.

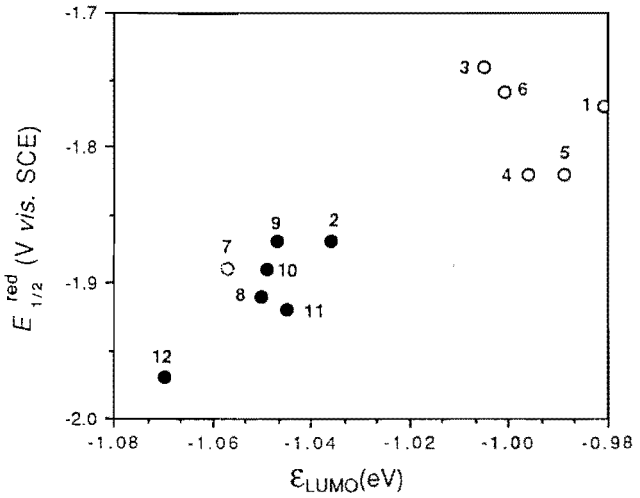


Figure 5. *A plot of half-wave reduction potential ($E^{re}_{1/2}$) against π-LUMO energies (ε_{LUMO}) for benz[c]acridines.*

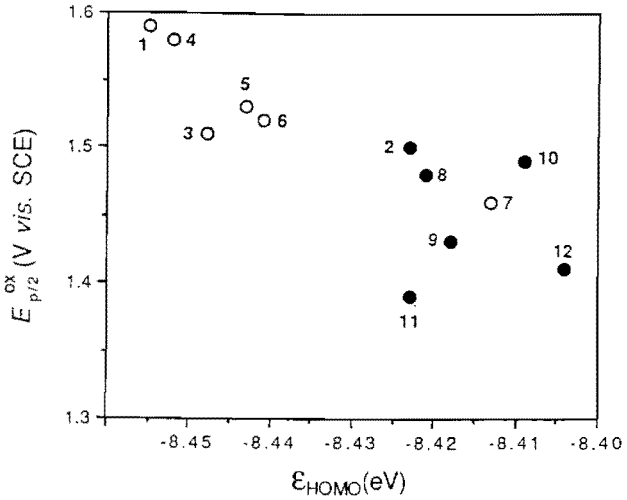


Figure 6. *A plot of half-peak wave oxidation potential ($E^{ox}_{p/2}$) against π-HOMO energies (ε_{HOMO}) for benz[c]acridines.*

The monomethylbenz[*c*]acridines (**2-6**) can be ranked in order of their MNDO heats of formation (ΔH_f, in kcal/mol unit) from the lowest to the highest as follows: **5** < **4** < **6** < **3** < **2**. The ΔH_f of the dimethylbenz[*c*]acridines (**7-10**), calculated by means of the MNDO method, was in order: 7,10-dimethylbenz[*c*]acridine (**9**, 69.67 kcal/mol) > 7,9-dimethylbenz[*c*]acridine (**8**, 70.12 kcal/mol) > 7,11-dimethylbenz[*c*]acridine (**10**, 71.38 kcal/mol) > 5,7-dimethylbenz[*c*]acridine (**7**, 73.04 kcal/mol) Table VIII).

*(5) Calculation of RE and REPE on benz[c]*acridine *(1) and its two derivatives (1_k, 1_M):* The resonance and resonance energy per π-electron of some selected benz[*c*]acridines were compared. Table IX shows the RE and REPE on the geometrical structures of benz[*c*]acridine (**1**), which has 18 π-electrons, and its two derivatives ($\mathbf{1_k}$, $\mathbf{1_M}$) which have 16 π-electrons.

The stability of the compounds measured by ß-value of RE was in the order: benz[*c*]acridine (**1**) (0.6322) > compound $\mathbf{1_k}$ (0.6027) > compound $\mathbf{1_M}$ (0.4511) (Table IX). However, ß value of REPE of benz[*c*]acridine ($\mathbf{1_k}$) (0.0377) was higher than that of the benz[*c*]acridine **1** (0.0351) and compound $\mathbf{1_M}$ (0.0282). This indicates that benz[*c*]acridine ($\mathbf{1_k}$) is the most stable and compound $\mathbf{1_M}$ is the most unstable.

*(6) Calculation of stability source for π-ring system of benz-[c]*acridine *(1):* The π-electron ring system in benz[*c*]acridine (**1**) consists of 10 π-ring components ($\mathbf{r_1}$-$\mathbf{r_{10}}$) as shown in

Table III. *Calculated π-LUMO coefficients of benz[c]acridines in Figure 1 (MNDO).*

Compd.	C-1	C-2	C-3	C-4	C-4a	C-5	C-6	C-6a	C-7	C-7a	C-8	C-9	C-10	C-11	C-11a	N-12	C-12a	C-12b
1	-0.024	-0.210	0.154	0.109	-0.249	-0.256	0.279	0.192	-0.463	0.090	0.278	-0.205	-0.222	0.270	0.134	-0.332	0.146	0.252
2	-0.019	-0.201	0.139	0.113	-0.233	-0.263	0.270	0.216	-0.476	0.102	0.269	-0.206	-0.212	0.263	0.132	-0.333	0.140	0.241
3	0.021	0.202	-0.145	-0.109	0.237	0.254	-0.270	-0.201	0.459	-0.077	-0.290	0.218	0.228	-0.281	-0.142	0.331	-0.137	-0.242
4	-0.030	-0.203	0.156	0.103	-0.248	-0.246	0.273	0.184	-0.466	0.101	0.291	-0.220	-0.211	0.270	0.123	-0.333	0.157	0.249
5	0.016	0.209	-0.144	-0.115	0.241	0.264	-0.278	-0.210	0.459	-0.067	-0.274	0.186	0.241	-0.278	-0.152	0.331	-0.129	-0.246
6	0.030	0.201	-0.154	-0.103	0.242	0.244	-0.269	-0.184	0.461	-0.096	-0.290	0.212	0.235	-0.285	-0.124	0.330	-0.155	-0.244
7	0.008	0.193	-0.122	-0.117	0.217	0.279	-0.281	-0.228	0.480	-0 091	-0.269	0.195	0.223	-0.258	-0.155	0.328	-0.115	-0 226
8	0.027	0.197	-0.145	-0.107	0.234	0.254	-0.266	-0.206	0.476	-0.113	-0.280	0.220	0.199	-0.264	-0.115	0.332	-0.155	-0.240
9	-0.013	-0.202	0.133	0.117	-0.228	-0.272	0.271	0.232	-0.468	0.079	0.260	-0.186	-0.226	0.267	0.148	-0.333	0.127	0.239
10	-0.024	-0.197	0.142	0.108	-0.232	-0.256	0.265	0.209	-0.473	0.105	0.278	-0.210	-0.221	0.272	0.119	-0.330	0.150	0.237
11	-0.025	-0.197	0.142	0.109	-0.231	-0.256	0.264	0.213	-0.470	0 099	0.279	-0.211	-0.211	0.273	0.122	-0.333	0.149	0.237
12	-0.034	-0.190	0.147	0.098	-0.233	-0.242	0.259	0.193	-0.474	0.122	0.290	-0.230	-0.203	0.275	0.098	-0.330	0.168	0.237

Table IV. *Calculated π-HOMO coefficients of benz[c]acridines in Figure 1 (MNDO).*

Compd.	C-1	C-2	C-3	C-4	C-4a	C-5	C-6	C-6a	C-7	C-7a	C-8	C-9	C-10	C-11	C-11a	N-12	C-12a	C-12b
1	0.163	0.302	0.056	-0.243	-0.254	0.356	0.369	-0.234	-0.330	0.026	0.258	0.137	-0.236	-0.255	0.117	0.245	-0.067	-0.209
2	-0.149	-0.293	-0.062	0.231	0.251	-0.348	-0.361	0.241	0.345	-0.008	-0.263	-0.148	0.229	0.258	-0.107	-0.252	0.057	0.212
3	0.157	0.295	0.056	-0.236	-0.249	0.349	0.361	-0.232	-0.328	0.026	0.274	0.152	-0.239	-0.266	0.112	0.247	-0.063	-0.206
4	0.155	0.297	0.061	-0.235	-0.253	0.349	0.364	-0.228	-0.332	0.017	0.274	0.154	-0.234	-0.266	0.107	0.251	-0.058	-0.211
5	0.163	0.297	0.052	-0.242	-0.247	0.355	0.363	-0.242	-0.326	0.039	0.256	0.124	-0.251	-0.264	0.122	0.243	-0.071	-0.202
6	-0.147	-0.291	-0.064	0.229	0.250	-0.342	-0.358	0.224	0.329	-0.016	-0.277	-0.153	0.250	0.283	-0.097	-0 252	0 052	0.210
7	-0.158	-0.288	-0.048	0.237	0.234	-0.365	-0.368	0.245	0.339	-0.017	-0.252	-0.134	0.230	0.247	-0.123	-0.243	0.075	0.199
8	0.140	0.290	0.069	-0.223	-0.252	0.342	0.358	-0.235	-0.348	0.001	0.273	0.162	-0.225	-0.265	0.096	0.256	-0.046	-0.215
9	-0.151	-0.290	-0.058	0.231	0.245	-0.349	-0.358	0.246	0.339	-0.022	-0.258	-0.132	0.244	0.263	-0.112	-0.248	0.060	0.207
10	-0.134	-0.283	-0.070	0.216	0.247	-0.336	-0.351	0.233	0.347	-0.000	-0.279	-0.165	0.239	0.281	-0.086	-0.257	0.040	0.213
11	0.140	0.287	0.067	-0.224	-0.249	0.340	0.355	-0.237	-0.342	0.009	0.273	0.156	-0.235	-0.273	0.096	0.255	-0.045	-0.210
12	0.116	0.274	0.081	-0.198	-0.247	0.320	0.342	-0.218	-0.349	-0.017	0.301	0.192	-0.234	-0.298	0.062	0.266	-0.017	-0.220

Table V. *Electron densities of benz[c]acridines (1-12).*

Compd.	C-1	C-2	C-3	C-4	C-4a	C-5	C-6	C-6a	C-7	C-7a	C-8	C-9	C-10	C-11	C-11a	N-12	C-12a	C-12b
1	4.005	4.072	4.044	4.052	4.029	4.040	4.037	4.099	3.967	4.099	4.031	4.062	4.049	4.035	3.931	5.226	3.892	4.034
2	4.005	4.072	4.045	4.051	4.032	4.039	4.043	4.081	4.004	4.078	4.036	4.062	4.052	4.033	3.935	5.226	3.895	4.032
3	4.006	4.072	4.045	4.053	4.029	4.041	4.038	4.099	3.970	4.078	4.075	4.041	4.056	4.030	3.936	5.222	3.894	4.034
4	4.005	4.072	4.044	4.053	4.028	4.041	4.038	4.102	3.966	4.096	4.011	4.109	4.033	4.038	3.930	5.223	3.892	4.035
5	4.005	4.072	4.045	4.053	4.029	4.041	4.038	4.099	3.968	4.095	4.035	4.046	4.092	4.014	3.937	5.225	3.893	4 034
6	4.005	4.072	4.045	4.053	4.029	4.042	4.037	4.100	3.966	4.101	4 027	4.066	4.033	4.073	3.914	5.229	3.890	4.034
7	4.005	4.073	4.044	4.056	4.010	4.080	4.022	4.085	4.011	4.079	4.036	4.062	4.051	4.034	3.932	5.226	3.893	4.037
8	4.004	4.072	4.045	4.051	4.031	4.039	4.043	4.081	4.003	4.081	4.016	4.104	4.034	4.037	3.932	5.227	3.894	4.033
9	4.005	4.072	4.045	4.051	4.032	4.039	4.042	4.076	4.006	4.074	4.040	4.046	4.092	4.013	3.942	5.223	3.897	4.032
10	4.004	4.072	4.045	4.051	4.032	4.039	4.042	4.083	4.004	4.081	4.034	4.067	4.033	4.071	3.914	5.237	3.890	4.032
11	4.005	4.072	4.045	4.051	4.031	4.039	4.042	4.080	4.005	4.079	4.019	4.086	4.074	4.017	3.935	5.229	3.893	4.033
12	4.004	4.072	4.045	4.052	4.031	4.040	4.042	4.083	4.002	4.082	4.014	4.107	4.019	4.074	3.914	5 230	3.892	4.032

Table VI. *π-Electron densities of benz[c]acridines (1-12).*

Compd.	C-1	C-2	C-3	C-4	C-4a	C-5	C-6	C-6a	C-7	C-7a	C-8	C-9	C-10	C-11	C-11a	N-12	C-12a	C-12b
1	0.952	1.008	0.983	1.006	1.000	0.996	1.002	1.054	0.928	1.054	0.994	1.002	0.986	0.931	0.941	1.163	0.909	1.031
2	0.952	1.007	0.984	1.005	1.002	0.994	1.005	1.048	0.946	1.047	0.995	1.001	0.988	0.990	0.946	1.158	0.913	1 029
3	0.952	1.008	0.983	1.006	1.000	0.996	1.002	1.052	0.930	1.050	1.013	0.991	0.990	0.985	0.942	1.162	0.912	1.031
4	0.952	1.008	0.983	1.006	1.000	0.996	1.002	1.055	0.926	1.055	0.984	1.020	0.983	0.993	0.938	1.164	0.909	1.032
5	0.953	1.007	0.983	1.006	1.000	0.996	1.002	1.053	0.929	1.051	0.996	0.998	1.005	0.981	0.943	1.162	0.910	1.032
6	0.953	1.008	0 983	1.006	1.000	0.996	1.002	1.056	0.927	1.056	0.991	1.004	0.978	1.008	0.934	1.165	0.910	1.032
7	0.951	1.009	0.982	1.009	0.997	1.013	0.993	1.051	0.943	1.049	0.996	1.001	0.987	0.991	0.942	1.159	0.911	1.033
8	0.952	1.007	0.984	1.005	1.002	0.994	1.005	1.048	0.945	1.049	0.986	1.019	0.984	0.992	0.943	1.158	0.912	1.029
9	0.952	1.007	0.984	1.005	1.002	0.993	1.005	1.044	0.948	1.043	1.002	0.995	1.007	0.977	0.950	1.157	0.913	1.029
10	0.952	1.007	0.984	1.005	1.002	0.994	1.004	1.048	0.945	1 049	0.992	1.003	0.980	1.008	0.943	1.160	0.912	1.029
11	0.951	1.008	0.983	1.005	1.002	0.994	1.005	1.047	0.947	1.045	0.989	1.015	1.002	0.983	0.944	1.158	0 912	1.030
12	0.952	1.008	0.983	1.005	1.002	0.994	1.004	1.049	0.944	1.051	0.984	1.020	0.976	1.009	0.938	1.161	0 912	1.029

Table VII. *Electronic transition (eV) in the ultraviolet region of compounds (1 and 3).*

benz[c]acridine (1)			8-methylbenz[c]acridine (3)		
E[a]	f[b]	nature	E[a]	f[b]	nature
3.60	0.140	π_1-π_1^*, π_2-π_1^*	3.60	0.137	π_1-π_1^*, π_2-π_1^*
3.93	0.183	π_1-π_1^*	3.89	0.201	π_1-π_1^*
4.13	0.002	n_0-π_1^*	4.15	0.002	n_0-π_1^*
4.47	0.231	π_2-π_4^*	4.47	0.024	π_2-π_3^*
4.60	1.492	π_2-π_2^*, π_1-π_3^*	4.55	1.402	π_3-π_1^*
4.90	0.696	π_2-π_3^*, π_3-π_2^*	4.78	0.956	π_3-π_1^*
5.02	0.161	π_3-π_2^*	4.99	0.071	π_1-π_3^*
5.20	0.467	π_2-π_3^*, π_1-π_4^*	5.18	0.420	π_2-π_2^*, π_1-π_3^*
5.67	0.171	π_1-π_5^*	5.40	0.030	π_2-π_5^*
5.90	0.268	π_4-π_2^*	5.63	0.240	π_1-π_4^*
5.98	0.340	π_3-π_3^*	5.76	0.017	π_1-π_5^*, π_2-π_4^*

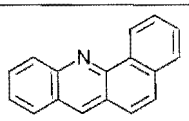
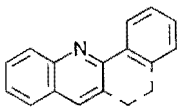
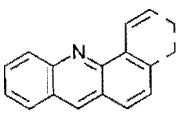
[a] E (eV) is the energy of the transitions. [b] (dimensionless) is the oscillator strenght.

Table VIII. *The heats of formation and resonance energies of benz[c]acridines (1-12).*

Compd.	ΔH_f (in kcal/mol)[a]	RE (in ß uniti)[b]
1	78.46	0.6322
2	77.35	0.6340
3	73.40	0.6266
4	71.71	0.6292
5	70.88	0.6264
6	72.93	0.6296
7	73.04	0.6323
8	70.12	0.6313
9	69.67	0.6281
10	71.38	0.6317
11	65.48	0.6257
12	65.07	0.6288

[a] ΔH_f: Heats of formation calculated by MNDO.
[b] RE: Resonance energy calculated by HMO.

Table IX. *Resonance energy (RE) and resonance energy per π-electron (REPE) of benz[c]acridine (1).*

Compd's No.	Compound's structure	Numbers of π-electron	RE[a]	REPE[b]
1		18	0.6322	0.0351
1k		16	0.6027	0.0377
1m		16	0.4511	0.0282

a) RE: Resonance energy (in β unit). b) REPE: Resonance energy per π-electron (in β unit).

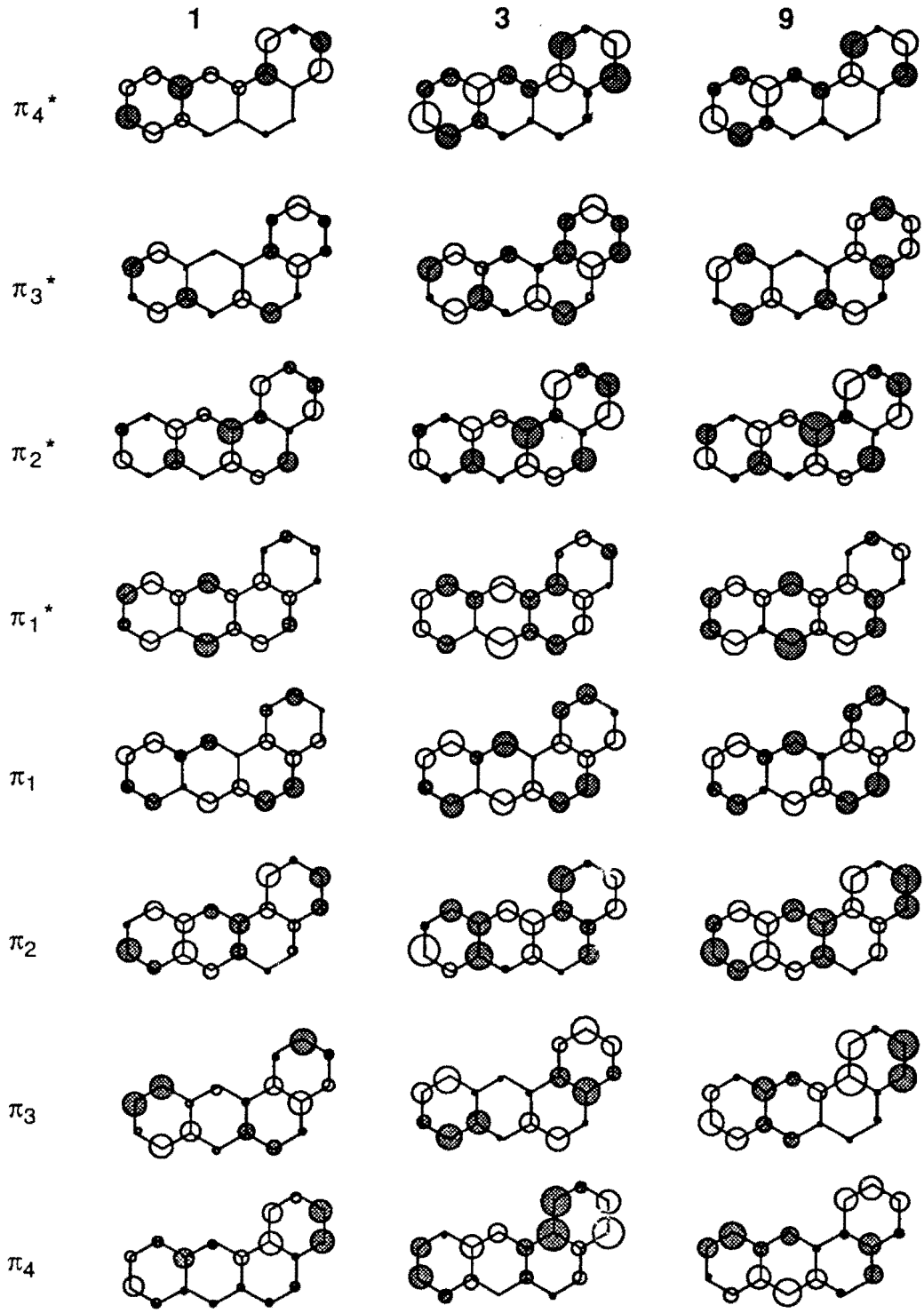


Figure 7. *Topology of the frontier orbitals of compounds (1,3,and 4) (CNDO/S-CI). Sizes of circles are roughly proportional to the coefficients.*

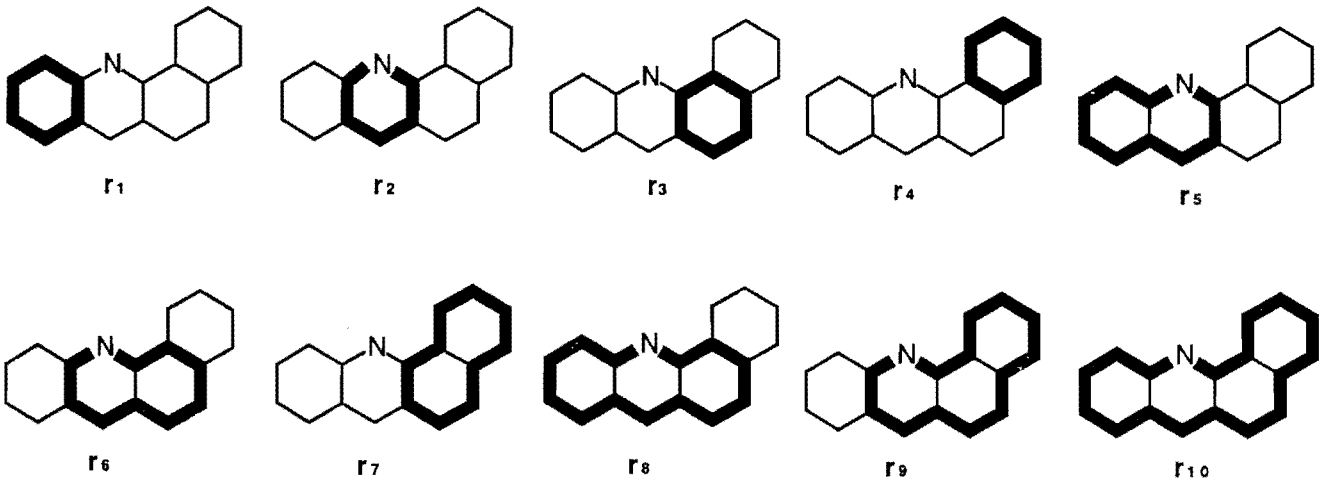


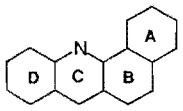
Figure 8. *Geometrically nonidentical π-electron circuits of ten components (r_1-r_{10}) of benz[c]acridine (1).*

Table X. *Circuit resonance energy (CRE) and circuit current (CC) of benz[c]acridine (1).*

System of benz[c]acridine (1)	CRE[a]	CC[b]
r_1	0.10367	0.46653
r_2	0.06911	0.31098
r_3	0.06781	0.30513
r_4	0.04612	0.20754
r_5	-0.00804	-0.03620
r_6	-0.00341	-0.03070
r_7	0.03749	0.33745
r_8	-0.00127	-0.01139
r_9	-0.00127	-0.01708
r_{10}	0.00747	0.10090

[a] CRE: Circuit resonance energy (in ß unit). +, aromatic ring; -, antiaromatic ring.
[b] CC: Circuit current (in Io unit). Benzene as the standard is 1.0 Io unit. +, diatropic; -, paratropic.

Table XI. *Bond current (BC) of benz[c]acridine (1).*



Ring	Bond current (in Io unit)
A	+0.62881[a]
B	+0.68432
C	+0.31652
D	+0.51985

a) +, diatropic.

Figure 8. Each CRE and CC of 10 components (r_1-r_{10}) in benz[c]acridine (**1**) was calculated by Aihara's graph theory of aromaticity.

Benz[c]acridines (**1**) is composed of four components of one π-electron ring system (r_1-r_4) (Figure 8). The CRE of r_1-r_4 are predicted to be aromatic, showing positive REs (Table X). Their calculated values of CC are also expressed by ring currents of benzene (Io). The (+) Io and (-) Io signs represent diatropism and paratropism, respectively (Table X). CRE and CC values of four components (r_1-r_4) were positively related with each other.

Benz[c]acridine (**1**) is composed of three components of two π-electron ring system (r_5-r_7) (Figure 8). The component r_7 which had an aromatic two π-electron ring system showed (+) ß value of CRE (Table X). Two components r_5 and r_6, which had a hetero two π-electron ring system, showed (-) ß values (Table X). CRE and CC values of these three components were positively related with each other.

Benz[c]acridine (**1**) is composed of two components of three π-electron ring system (r_8,r_9) (Figure 8). The CRE of r_8 and r_9, which had a π-electron ring system with three hetero atoms, showed (-) ß value (Table X). The CRE and CC values of these two components were positively related with each other.

Benz[c]acridine (**1**) is composed of a single component of four π-electron ring system (r_{10}) (Figure 8). Although this component has a hetero four π-electron ring system, it showed (+) ß value of CRE (Table X). The CC value of component r_{10} also showed (+) Io value.

(7) Calculation of BC value on four rings of benz[c]acridine (1): All four (**A,B,C,D**) of benz[c]acridine (**1**) showed (+) Io values of BC (Table XI). This indicated that four rings are diatropism (+).

From the above calculations, the stability of the π-electron

Table XII. *Resonance energy per π-electron (REPE) of compounds (1-12).*

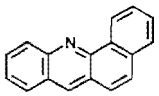
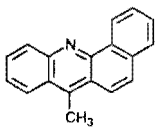
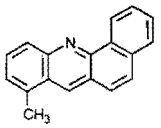
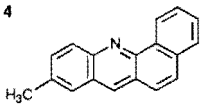
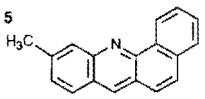
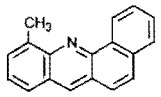
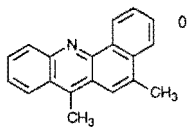
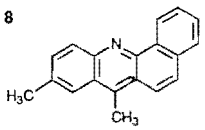
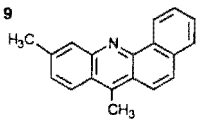
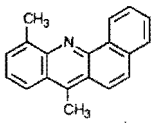
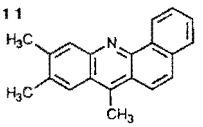
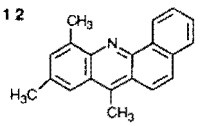
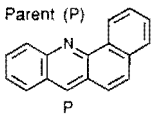
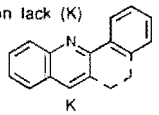
Compd's No.		P[a]	K[b]	ΔPK[c]	ΔPM[d]	Carcinogenicity index[e]
1		0.0351	0.0377	-0.0026	0.0069	-
2		0.0317	0.0334	-0.0017	0.0064	+
3		0.0313	0.0332	-0.0019	0.0065	-
4		0.0315	0.0333	-0.0018	0.0066	-
5		0.0313	0.0331	-0.0018	0.0066	-
6		0.0315	0.0333	-0.0018	0.0066	-[f]
7		0.0287	0.0334	-0.0047	0.0061	-
8		0.0287	0.0299	-0.0012	0.0061	+

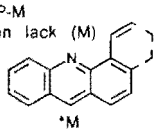
Table XII *(continued). Resonance energy per π-electron (REPE) of compounds (1-12).*

9		0.0286	0.0297	-0.0011	0.0062	+
10		0.0287	0.0299	-0.0012	0.0061	+
11		0.0261	0.0269	-0.0008	0.0058	+
12		0.0262	0.0271	-0.0009	0.0058	+

a) Parent (P) 

b) K-region lack (K) 

c) ΔPK=P-K

d) ΔPM=P-M
M-region lack (M) 

e) Skin tumor-producing activity (ref:3): + active; - inactive.

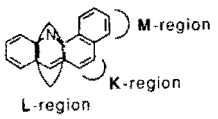
f) ref: 19.

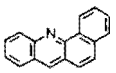
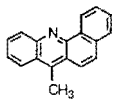
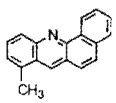
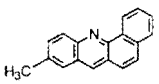
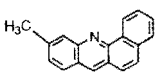
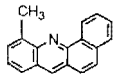
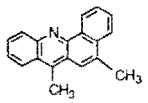
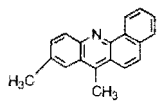
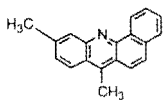
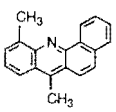
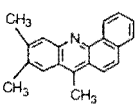
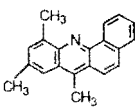
system of benz[*c*]acridine (**1**) consists of three ring systems, benzene (which has aromatic 6 π-electrons), pyridine (which has hetero 6 π-electrons), and naphthalene (which has aromatic 10 π-electrons).

*(8) Relationship between carcinogenic activity and π-electron density of benz[c]*acridine *(1):* The calculated REPE values of benz[*c*]acridines (**2-12**), and their corresponding analogues ($\mathbf{2_K}$-$\mathbf{12_K}$ and $\mathbf{2_M}$-$\mathbf{12_M}$) which lack the double bond in the K- or M- region respectively, are given in Tables XII and XII (continued). In all cases, the REPE values for the compounds $\mathbf{2_K}$-$\mathbf{12_K}$ which lack the double bond in the K-region were greater than those of their corresponding parent compounds. On the other hand, the REPE values for the $\mathbf{2_M}$-$\mathbf{12_M}$ which lack the double bond in the M-region were smaller than those of their corresponding parent compounds. Tables XII and XII (continued) show that 7-methylbenz[*c*]acridine (**2**), 7,9-dimethylbenz[*c*]acridine (**8**), 7,10-dimethylbenz[*c*]acridine (**9**), 7,11-dimethylbenz[*c*]acridine (**10**), 7,9, 10-trimethylbenz-[*c*]acridine (**11**) and 7,9, 11-trimethylbenz[*c*]acridine (**12**) except 5,7-dimethylbenz[*c*]acridine (**7**) showed potent carcinogenic activity, as is shown in Table XII (3,19). It is interesting to note that these compounds (**8-12**), except compound **2**, had a significantly lower REPE value, as compared with the REPE value of benz[*c*]acridine (**1**), 8-methylbenz[*c*]acridine (**3**), 9-methylbenz[*c*]acridine (**4**), 10-methylbenz[*c*]acridine (**5**), and 11-methylbenz[*c*]acridine (**6**), which had no carcinogenic activity. It is thus concluded that benz[*c*]acridines with methyl groups introduced at position 7 showed carcinogenic activity and lower REPE value. Table XIII shows the comparisons of the degrees of carcinogenesis with charge of K-region (QK), charge of nitrogen atom (QN), charge of L-region (QL), and charge of M-region (QM). The carcinogenic activity appeared to be related to the charges of QK, QN, QL, and QM. For example, benz[*c*]acridines (**1-12**) could be divided into the carcinogenic group (**2, 8-12**) with increasing electron density (HMO) (2.0024) except compound **7**, and the noncarcinogenic group (**1, 3-6**) with decreasing electron density (HMO) (1.9990)(3,20).

(9) Dipole moment and retention times: Table XIV shows the

Table XIII. *Carcinogenicity and charges of benz[c]acridines in some representative regions of molecular orbitals.*



Compd's No.	Structure	Charge of K-region (QK)	Charge of nitrogen atom (QN)	Charge of L-region (QL)	Charge of M-region (QM)	Carcinogenicity epithelioma index (%)[a]
1		1.9980[b] 1.9984[c] 1.9982[d]	1.3472 1.1630 1.3472	2.2237 2.0911 2.2238	1.9865 1.9888 1.9866	-
2		2.0025 1.9985 -	1.3644 1.1577 -	2.2591 2.1032 -	1.9886 1.9891 -	63
3		1.9987 1.9951 1.9984	1.3504 1.1619 1.3504	2.2248 2.0918 2.2236	1.9869 1.9890 1.9868	0
4		1.9979 1.9983 -	1.3461 1.1636 -	2.2271 2.0901 -	1.9868 1.9889 -	0
5		1.9990 1.9982 1.9990	1.3515 1.1624 1.3504	2.2282 2.0914 2.2286	1.9870 1.9887 1.9876	0
6		1.9975 1.9984 -	1.3437 1.1653 -	2.2233 2.0922 -	1.9868 1.9882 -	?
7		2.0436 2.0053 -	1.3635 1.1594 -	2.2650 2.1021 -	1.9876 1.9916 -	0
8		2.0028 1.9985 2.0019	1.3633 1.1584 1.3640	2.2621 2.1033 2.1974	1.9890 1.9890 1.9890	81
		2.0038[b] 1.9982[c] 2.0032[d]	1.3684 1.1569 1.3694	2.2633 2.1048 2.1984	1.9890 1.9890 1.9890	56
		2.0024 1.9986 2.0026	1.3610 1.1595 1.3616	2.2585 2.1046 2.1938	1.9890 1.9891 1.9890	14
		2.0042 1.9984 -	1.3674 1.1580 -	2.2666 2.1048 -	1.9895 1.9887 -	48
		2.0027 1.9984 -	1.3600 1.1607 -	2.2616 2.1048 -	1.9893 1.9889 -	29

a) Ref.3. b) Hückel molecular orbital (HMO).
c) Modified-neglect-of-diatomic overlap (MNDO).
d) Ref.20.

Table XIV. *Calculated dipole moments (μ, in Debye units) and retention times of benz[c]*acridines (*1-12*)

Compd's No.	$\mu_{point\ charge}$	μ_{hybrid}	μ_{total}[a]	Retention time LiChrosorb RP-8 (7μm)[b]
1	0.223	1.113	1.336	1.00
2	0.346	1.034	1.379	1.24
3	0.274	1.036	1.310	1.24
4	0.285	1.084	1.368	1.26
5	0.169	1.171	1.326	1.22
6	0.158	1.206	1.328	1.88
7	0.397	0.999	1.396	1.65
8	0.381	1.006	1.383	1.57
9	0.260	1.088	1.339	1.57
10	0.253	1.137	1.377	2.34
11	0.317	1.066	1.340	1.99
12	0.304	1.094	1.389	3.11

a): $\mu_{total} = \mu_{point\ charge} + \mu_{hybrid}$. b) Ref. 21.

calculated dipole moments (μ, in Debye units, D) and retention times of benz[*c*]acridines **(1-12).** On their retention times of reversed-phase liquid chromatography (RPLC) on prepacked LiChrosorb RP-8 (7 μm), carcinogenic benz[*c*]acridines **(2, 8-12)** with the increasing molecular weight and the increasing μ_{total} values of the calculated dipole moments (polarity) were not apparently parallel to their increasing retention times (Table XIV) (21). RPLCs of LiChrosorb RP-18 (10 μm), LiChrosorb RP-18 (5 μm), Zorbax C-18 showed also similar trends (data not shown) (21).

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